SYNTHESIS OF DIFFERENT HETEROBICYCLIC SYSTEMS WITH DOMINO-HECK REACTIONS

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Abstract

It has been shown that imides and its derivatives like isoindolines which are active precursors of the important compounds in the pharmacological and medicinal researches have antidepressant, anticancer, antimalarial, antibacterial and fungicidal properties (Brana 2001; Zentz 2002).

Furthermore, the arylation and alkenization of alkenes in presence of palladium catalyst in organic synthesis named as Heck reaction, keep their currency as very effective catalyzing method in forming carbon-carbon bonds. Recently, the asymmetric Heck-type hydroarylation of specific bicyclic ring systems of alkenes have been examined intensively, because of the easily obtained stereoselective results (Namyslo & Kaufmann 1997, 1999).

This study planned after a wide literature surveys, is consist of three steps. The first step is the synthesizing of tricyclic imides and the second one is including after reducing of these compounds with $NaBH_4$ to obtain the new bicylic derivatives. The third step is domino-Heck reactions of alkenic imides with aryl (hetaryl) halides.

Key words: *tricyclic imides, reduction of hydrite, domino-heck type hydroarylation reactions*

1. INTRODUCTION

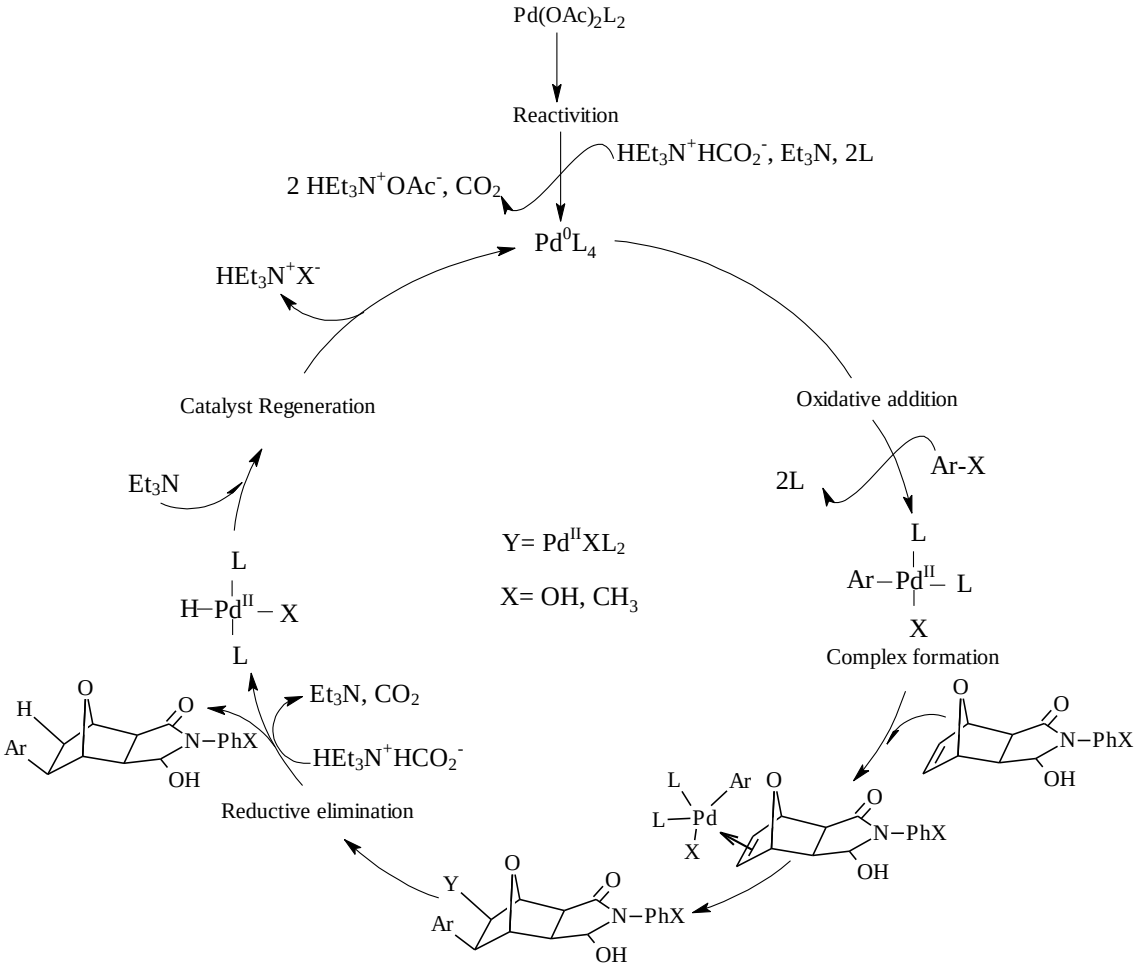
Due to its broad synthetic potential as a stereoselective C-C coupling method the Heck reaction has been the subject of several synthetic and mechanistic studies over the last 35 years (Heck 1985; De Meijere et al. 1995; Tsuji 1996; Cheprakov et al. 2000; Cheprakov et al. 2002). Originally developed to arylate acyclic alkenes, the reaction scope has been extended to cyclic compounds later, too. Rigid bi- and higher cyclic systems make the catalytic, oxidative Heck-coupling reaction impossible. When the catalytic precursor of a Heck reaction is $Pd(OAc)_2$ associated with 3 equiv PPh_3, the active species is $Pd^0(PPh_3)_2(OAc)^-$, generated in stoichiometric amount (Amatore et al. 2005). Consequently, in Heck reactions when the catalytic precursor is $Pd(OAc)_2$ associated with PPh_3, the alkene play a dual role, as illustrated in Scheme 1.

To circumvent this problem, domino-Heck reactions were introduced with a hydroarylation reaction as its simplest variant (Arcadi et al. 1989; Larock et al. 1989), leading to a reductive C-C-coupling reaction. Kaufmann and his research group have been carrying out new examples of reductive Heck reactions using bicyclic systems aiming at the synthesis of new biologically active compounds (Namyslo & Kaufmann 1997, 1999). In addition, *N*-substituted imides, such as maleimides (Zentz 2002) and especially bicyclicand tricyclic derivatives such as tandospirone derivatives (Kossakowski et al. 2008) are known for their broad spectrum of pharmacological properties, thus showing antibiotic, fungicidal, analgesic, anxiolytic and cytostatic effects.

In our previous works we have accomplished palladium-catalyzed domino-Heck applications of bicyclic and tricyclic precursors of epibatidine analogs (Yolacan et al. 2006). We then focused on reductive Heck reactions of polyfunctional tricyclic molecules with a strained C=C bond and an N-acylamino imide group (Bagdatli et al. 2007).

Later, we became interested in the synthesis of bioactive norcantharidin analogues that represent aryl-modified bicyclic imide systems, too. We had first synthesized endo-N-phenylbicyclo[2.2.1]hept-5-ene-2,3-dicarboximide and exo-N-phenyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide as starting compounds. We then investigated their hydroarylation reactions with aryl- and hetaryl iodides in the presence of triphenylarsine giving and subsequent reduction reactions by $LiAlH_4$ to open a new access

to perhydroisoindole derivatives. In reductive arylation reactions triphenylarsine has proved to be superior to triphenylphosphine and carbenes as ligands in both, selectivity and yield (Celik et al. 2009).



Scheme 1. The whole process is a catalytic cycle

2. EXPERIMENTAL

2.1. General

The starting chemicals were of analytical grade and provided from either Merck or Sigma-Aldrich companies.

All reactions were conducted under N_2 and carried out in a *Schlenk* system. Column chromatography (CC): silica gel *60*. TLC: silica gel precoated (0.2 mm layer) aluminium sheets (*Merck*). M.p.: *Gallenkamp*-melting-point-apparatus; uncorrected. IR Spectra: *Perkin- Elmer FT-IR* spectrometer; KBr pellets; in cm^{-1}. NMR Spectra: *Bruker- Digital-FT-NMR-Avance* (400 MHz) and *Varian Inova* (500 MHz) spectrometers; $CDCl_3$ solns.; δ in ppm rel. to $SiMe_4$ as internal standard, *J* in Hz.

2.2. General Procedure of Regioselective Reduction of 5,6 : To a refluxing solution of imide **5** or **6** (0.14 mmol) in methanol (4 mL) was added $NaBH_4$ (2.80 mmol) and the reaction was further refluxed for 30 min under stiring. After saturated aqueous sodium bicarbonate was added to destroy the excess reduction agent at this temperature, organic solvents were removed under reduced pressure. The

residue was extracted with dichloromethane, and the combined organic extracts were washed with brine, dried, filtered and concentrated to organic layer in vacu followed by silica gel column chromatographic purification of obtained resudie using solvent mixture.

5-hydroxy-4-(4-methylphenyl)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (7): CC (AcOEt/hexane 3:1): (54%). Colorless crystals. M.p. 202°. IR: 3211, 2972, 2943, 1646, 1613, 1515, 1422, 1403, 1065, 819. ^{1}H-NMR (400 MHz): 1.40-1.38 (dd, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.70-2.66 (m, 2H, CH), 3.13 (s, H, CH), 3.21-3.19 (d, H, CH), 4.81 (s, H, CH), 6.04 (s, =CH), 6.18 (s,=CH), 7.09-7.11 (d, 2H, arom. H), 7.23-7.25 (d, 2H, arom. H). ^{13}C-NMR (100 MHz): 20.96 (CH_3), 45.08 and 45.62 (CH), 46.56 and 49.58 (CH), 51.06 (CH_2), 86.17 (CH-OH), 124.07 (Cm), 129.15 (Co), 129.34 (Cq-N), 134.37 and 134.93 (CH=CH), 135.87 (C-CH_3), 174.39 (C=0).

5-hydroxy-4-(4-hydroxyphenyl)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (8): CC (AcOEt/hexane 3:1): (48%). Bright crystals. M.p. 246°. IR: 3234, 2974, 2935, 1668, 1613, 1597, 1439, 1417, 1044, 820. ^{1}H-NMR (400 MHz): 1.37-1.40 (m, 2H, CH_2), 2.24-2.57 (m, 2H, CH), 3.09-3.11 (dd, 2H), 4.67 (s, 2H, CH), 6.05 (s, =CH), 6.18 (s, =CH), 6.38-6.40 (d, 2H, arom. H), 7.05-7.07 (d, 2H, arom. H). ^{13}C-NMR (100 MHz): 45.02 and 45.47 (CH), 46.62 and 49.26 (CH), 51.06 (CH_2), 86.60 (CH-OH), 115.39 (Cm), 126.61 (Co), 129.72 (Cq-N), 134.34 and 135.89 (CH=CH), 155.79 (C-OH), 174.24 (C=O).

2.3. General Procedure of Domino-Heck Reactions of 7, 8: $Pd(OAc)_2$ (5.6 mg, 25 μmol) and $AsPh_3$ (55 μmol) were dissolved in anh. DMF (3 ml) and the soln. was stirred at 40° for 15 min. Then, **7** or **8** (1 mmol), the aryl compound (1.5 mmol), Et_3N (488 μl, 3.50 mmol), and trimethylsilylacetylene or phenylacetylene (3 mmol) were added rapidly in one portion. The mixture was kept at the same temperature for 24 h. After cooling to r.t., brine (50 ml) was added, the mixture was extracted with AcOEt and dried ($MgSO_4$). The solvent was evaporated and the residue purified by CC.

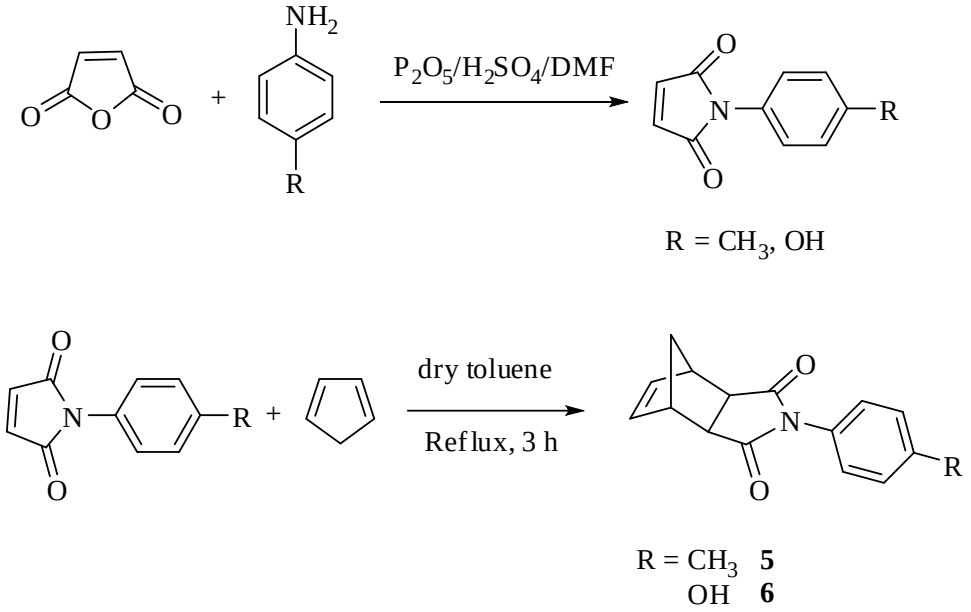
5-Hydroxy-4-(4-methylphenyl)-5-phenyl-6-trimethylsilylethynyl-4-azatricyclo-[5.2.1.0^{2,6}]dekan-3-on (9): CC (AcOEt/hexane 4:1): (38%). Colorless crystals. M.p. 189°. IR: 3328, 2965, 2167, 1668, 1513, 1427, 1246, 1071, 841, 785, 698. ^{1}H-NMR (400 MHz): 0.01 (s, 9H, CH_3), 1.79-1.82 (d, 2H, CH), 2.55 (s, 3H, -CH_3), 270-2.72 (d, 2H, CH_2), 3-32-3.24 (d, 2H, CH), 5.53 (s, H, -OH), 7.29-7.59 (m, 9H, arom. H). ^{13}C-NMR (100 MHz): 0.00 (Si-CH_3), 21.43 (CH_3), 39.02 and 39.74 (CH), 44.30 and 44.44 (CH), 47.22 (CH_2), 86.09 (CH-OH), 107.04 (-C≡C), 124.63 (Cm), 126.47 (Co), 129.02 (Cq-N), 134.96 (C-CH_3), 142.10 (Cq-C), 175.13(C=0).

5-Hydroxy-4-(4-hydroxyphenyl)-5-methoxyphenyl-6-trimethylsilylethynyl-4-azatricyclo-[5.2.1.0^{2,6}]dekan-3-on (10): CC (AcOEt/hexane 3:1): (40%). Colorless crystals. M.p. 214°. IR: 3539, 3366, 2961, 2168, 1679, 1610, 1512, 1463, 1431, 1241, 1036, 836, 760, 697. ^{1}H-NMR (400 MHz): 0.00 (s, 9H, CH_3), 1.38-1.41 (d, 2H, CH), 2.41 (s, 3H, -CH_3), 292-2.98 (m, 2H, CH_2), 3.90 (s, 3H, -OCH_3), 4-23-4.25 (d, 2H, CH), 5.34 (s, H, -OH), 6.74-7.24 (m, 9H, arom. H). ^{13}C-NMR (100 MHz): 0.00 (Si-CH_3), 30.03 and 39.75 (CH), 44.49 and 45.98 (CH), 47.44 (CH_2), 55.64 (-OCH_3), 60.77 (CH-OH), 113.50 (-C≡C), 127.59 (Cm), 127.86 (Co), 128.02 (Cq-N), 158.25 (Cq-C), 175.95 (C=0).

3. RESULTS AND DISCUSSION

In this study, the conventional technique was used to synthesize two imides by the reaction of maleic anhydride with p-aminophenol and p-toluidine, respectively, in the presence of diphosphorus pentoxide (P_2O_5) as a catalyst, which decreased the temperature needed for ring closure from 20 °C to 70 °C according to the literature (Roderick et al. 1957; Park et al. 1992).

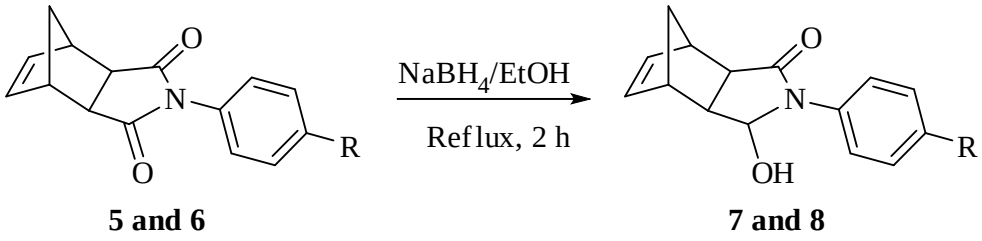
We have prepared *N*-(4-methylphenyl)-bicyclo[2.2.1]hept-5-ene-2-*exo*-2,3-dicarboximide **5** and *N*-(4-hydroxyphenyl)-bicyclo[2.2.1]hept-5-ene-2-*exo*-2,3-dicarboximide **6** as the starting compounds in yields (60% and 65%, respectively), Scheme 1 (Rulisek et al. 2005). NMR and IR spectra were also in agreement with the proposed structures. ^{1}H NMR spectra of **5** and **6** showed four aromatic protons at 6.99-7.22 and 6.73-6.90 ppm and two alkenic protons at 6.25 and 6.18 ppm.



Scheme 1. Synthesis of compounds **5, 6**

We obtained as the expected two new products from the same reaction. The resulting residues were purified by silica gel chromatography with a solvent gradient of (ethyl acetate/*n*-hexane) to afford the title compounds.

The structurally related perhydroisoindoles are selective sigma receptor antagonists and have a low potential for movement disorder side effects associated with typical antipsychotic agents (De Costa et al. 1993; Ciganek & Square 1993). Therefore, we have first reduced *N*-(4-methylphenyl)-bicyclo[2.2.1]hept-5-ene-2-*exo*-2,3-dicarboximide **5** and *N*-(4-hydroxyphenyl)-bicyclo[2.2.1]hept-5-ene-2-*exo*-2,3-dicarboximide **6** with $NaBH_4$ in ethanol at 78 °C to obtain **7** and **8**, Scheme 2.



Scheme 2. Synthesis of compounds **7, 8**

Regular work (HCl; CC) gave compound **7** in 80% good yield, its spectroscopic data and crystal structure were reported, recently Figure 1 (Aslantas et al. 2015).

Research in the field of domino-reactions is attracting considerable attention in synthetic organic chemistry since it enables the rapid assembly of complex molecules in one-pot processes (De Meijere et al. 1999). Very elegant examples of palladium-catalyzed cascade processes where a single catalytic cycle entails several sequential bond transformations have been recently reported (Arjana et al. 2004). In this work, we also would like to describe our results in the investigations on the palladium-catalyzed domino-*Heck*-type reactions of **7**, **8**.

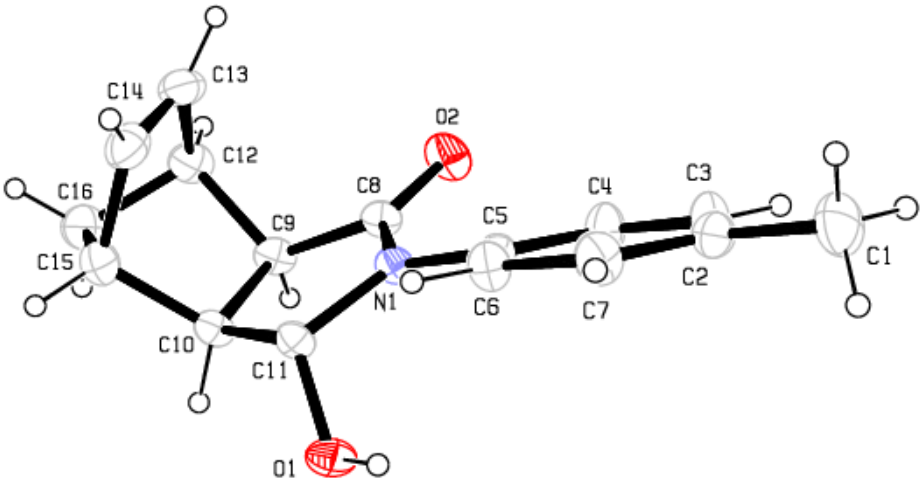
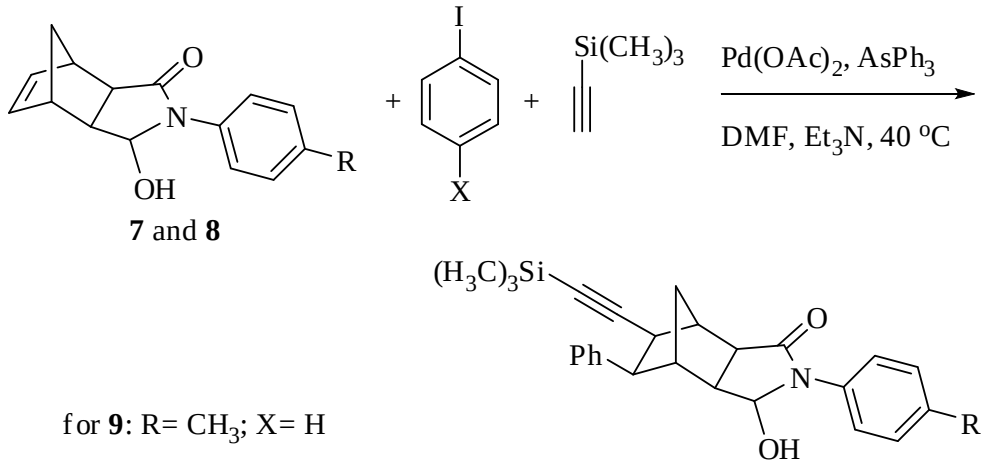


Figure 1. The molecular structure of the title compound, with atom labelling. Displacement ellipsoids are drawn at the 30% probability level

The use of phenylacetylene and trimethylsilylacetylene under domino-*Heck* conditions (Yolacan et al. 2006; Bagdatli et al. 2007), provided alkynic tricyclic imides.

Treatment of **7** with iodobenzene and trimethylsilylacetylene under reductive domino-Heck conditions and subsequent column chromatography on silica gel gave **9** as single product isolated yields of 38 % Scheme 3. We also synthesized **10** from **8** with 4-methoxy-1-iodobenzene and trimethylsilylacetylene under the same conditions.



7 and **8**

for **9**: R= CH_3; X= H

for **10** : R= OH ; X= OMe

9 and **10**

Scheme 3. Synthesis of compounds **9, 10**

The absent of bridge protons in the ^{1}H NMR spectra of **9** and **10** result confirmed the structure of new products. In addition to the ^{13}C-NMR and IR spectral data which were in agreement with the proposed structures.

4. CONCLUSION

We first synthesized N-phenylsubstituted adducts maleic anhydride with p-aminophenol and p-toluidine of the unsaturated imides by a reduction procedure to check the effect on both, the reactivity of the starting materials as well as the bioactivity of the products as Cantharidin analogues.

In conclusion, in the presence of triphenylarsine as a ligand the palladium-catalyzed hydroarylation of the easily accessible tricyclic *N*-phenyl derivatives of the unsaturated imides **7** and **8** has been proven to be a stereoselective, versatile and high-yield approach to the synthesis of aryl and heteroaryl derivatives of heterotricyclic systems. Domino-*Heck* C-C coupling reactions with aryl or heteroaryl halides have been shown to be feasible in the presence of trimethylsilylacetylene. Results have also demonstrated that the reductive access to aryl-substituted bridged hydroxypyrrolidinone derivatives will be useful for the construction of novel heterocycles of potential pharmacological interest.

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